

A Novel Strategy to Translate the Biomechanical Rupture Risk of Abdominal Aortic Aneurysms to their Equivalent Diameter Risk: Method and Retrospective Validation

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WHAT THIS PAPER ADDS

Reported biomechanical abdominal aortic aneurysm (AAA) rupture risk assessment studies suffer from severe limitations such as high operator variability, small sample sizes, and clinically difficult interpretation of the results. The present paper used a gender-specific computational method of low operator variability and tested the biomechanical rupture risk assessment on the largest patient cohort so far. The concept of equivalent diameters relates biomechanical results to basic conclusions drawn from large clinical AAA trials, and hence supports a sound clinical interpretation of biomechanical results. Finally, the retrospective and size-adjusted analysis verified that biomechanical risk indicators are higher in ruptured than non-ruptured cases.

Objective: To translate the individual abdominal aortic aneurysm (AAA) patient's biomechanical rupture risk profile to risk-equivalent diameters, and to retrospectively test their predictability in ruptured and non-ruptured aneurysms.

Methods: Biomechanical parameters of ruptured and non-ruptured AAAs were retrospectively evaluated in a multicenter study. General patient data and high resolution computer tomography angiography (CTA) images from 203 non-ruptured and 40 ruptured aneurysmal infrarenal aortas. Three-dimensional AAA geometries were semi-automatically derived from CTA images. Finite element (FE) models were used to predict peak wall stress (PWS) and peak wall rupture index (PWRI) according to the individual anatomy, gender, blood pressure, intraluminal thrombus (ILT) morphology, and relative aneurysm expansion. Average PWS diameter and PWRI diameter responses were evaluated, which allowed for the PWS equivalent and PWRI equivalent diameters for any individual aneurysm to be defined.

Results: PWS increased linearly and PWRI exponentially with respect to maximum AAA diameter. A size-adjusted analysis showed that PWS equivalent and PWRI equivalent diameters were increased by 7.5 mm ($p = .013$) and 14.0 mm ($p < .001$) in ruptured cases when compared to non-ruptured controls, respectively. In non-ruptured cases the PWRI equivalent diameters were increased by 13.2 mm ($p < .001$) in females when compared with males.

Conclusions: Biomechanical parameters like PWS and PWRI allow for a highly individualized analysis by integrating factors that influence the risk of AAA rupture like geometry (degree of asymmetry, ILT morphology, etc.) and patient characteristics (gender, family history, blood pressure, etc.). PWRI and the reported annual risk of rupture increase similarly with the diameter. PWRI equivalent diameter expresses the PWRI through the diameter of the average AAA that has the same PWRI, i.e. is at the same biomechanical risk of rupture. Consequently, PWRI equivalent diameter facilitates a straightforward interpretation of biomechanical analysis and connects to diameter-based guidelines for AAA repair indication. PWRI equivalent diameter reflects an additional diagnostic parameter that may provide more accurate clinical data for AAA repair indication.

Keywords: Aneurysms rupture, Biomechanical analysis, Aneurysm repair indication, Computer-based model, Risk assessment

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INTRODUCTION

The natural history of abdominal aortic aneurysms (AAAs) is determined by proteolytic degradation of elastin and collagen in the aortic wall resulting in dilatation and eventual rupture. AAA rupture has a total mortality between 75% and 90%, and death from ruptured AAAs ranks among the 10th leading cause of death in men above the age of 65.¹

The indication for elective AAA repair is determined by the likelihood of rupture.² Consequently an accurate evaluation of rupture risk is of vital importance in reducing aneurysm related mortality, without substantially increasing the rate of elective AAA repair.

Data on AAA rupture risk has been provided from different sources.³ According to the current clinical view, AAA rupture risk is based on the maximum diameter; a diameter of 55 mm or more is a generally accepted as indication for repair in males.^{3,4} This kind of rupture risk assessment is, however, undergoing discussions,^{5,6} since AAAs with a diameter less than 55 mm may rupture^{7,8} whereas many aneurysms larger than 55 mm may never rupture.⁸ Large AAA diameter is not the only risk factor, and rupture has also been associated with shape,⁹ female gender,^{10–13} family susceptibility,^{14–16} high mean arterial pressure (MAP), smoking,^{9,17} and fludeoxyglucose (FDG) uptake on positron emission tomography (PET).¹⁸ Nearly all large AAAs have intraluminal thrombus (ILT),¹⁹ which is associated with a weaker²⁰ and thinner²¹ underlying aneurysm wall, and ILT growth has been associated with risk of rupture.²² Consequently, the diameter criterion has clear limitations.

According to the biomechanical rupture risk hypothesis, an aneurysm ruptures if wall stress overcomes wall strength at a certain location in the wall.⁶ A biomechanical analysis is typically based on finite element (FE) predictions and such studies showed that peak wall stress (PWS)^{23,24} and peak wall rupture index (PWRI)^{25,26} discriminate better between ruptured and non-ruptured aneurysms than the maximum diameter. Specifically, the PWRI relates mechanical stress and strength of the aneurysm wall, and incorporates risk factors associated with aneurysm wall weakening including female gender, ILT thickness and large relative expansion with respect to the normal infrarenal diameter.²⁷ No clinical trial, however, has investigated threshold values of these parameters for AAA repair, consequently they have limited clinical relevance.

The present study used the concept of risk-equivalent diameters, i.e. where biomechanical rupture risk values are translated to equivalent diameters of the average aneurysm patient. Specifically, the average patient is defined as the mean response of our non-ruptured patient cohort weighted by the gender ratio of the UK small aneurysm trial.³ Retrospectively collected ruptured and non-ruptured cases were used to test to what extent biomechanical indices can discriminate among the groups.

METHODS

Patient cohort and data acquisition

Data from 40 ruptured and 203 non-ruptured aneurysmal infrarenal aortas from 229 patients (179 male and 50 female) were retrospectively considered for this study (Table 1). Patients underwent contrast-enhanced computed tomography angiography (CTA) of the aorta at Karolinska University Hospital and Sankt Göran Hospital in Stockholm, University Hospital and St Joseph Hospital of Liege, and University Hospital in Heidelberg at typical image resolutions (in-plane, from 0.39 mm to 0.8 mm; slice thickness, from 1.0 mm to 5.0 mm). A considerable portion of our cohort is not in the diameter range of primary clinical importance, 50 mm to 60 mm say, but investigating a larger diameter spectrum might help to identify reasons why some small AAA rupture whereas many large cases do not. Prior to CTA, patient data were recorded for non-ruptured cases, and for the ruptured cases blood pressure at the last admission before rupture was used. If this information was not available, blood pressure of 140/80 mmHg was considered. No gender differences for age and systolic/diastolic pressure among the different groups were recorded (Table 1). The female–male ratio was lower in the ruptured (6/34) than in the non-ruptured (44/159) group. CTA scans recorded with strongly inhomogeneous lumen intensity were a priori rejected to minimize user interactions to build the computational models. The collection and use of anonymized data from human subjects was approved by the local ethics committees.

Image reconstruction and biomechanical analysis

Aneurysms were reconstructed and analyzed with the diagnostic system A4clinics (VASCOPS GmbH, Graz, Austria). The reconstruction process used deformable image segmentation models and required minimal user interactions dependent on the complexity of the aneurysm and the quality of the image data. Centerline-based maximum diameter, PWS, and PWRI were calculated automatically. FE models that specifically account for the ILT, and the thinning of the aneurysm wall covered by it, were used; all modeling details have been reported elsewhere.^{21,25,28} The FE method is an established numerical concept that divides any geometry into a large number of small finite elements, which together define a (hypothetical) biomechanical model of the aneurysm. The hypothetical model (FE model) was pressurized by the mean arterial pressure (MAP; $1/3$ systolic pressure + $2/3$ diastolic pressure), which in turn predicted the mechanical stress (force per area) in the wall of the aneurysm. Apart from geometry and arterial pressure, a FE model requires constitutive descriptions for the wall and the ILT. A constitutive description is a mathematical model of biomechanical properties, which relates stress and strain (deformation) and/or describes the strength of the tissue. The FE models used in the present analysis considered isotropic constitutive descriptions for the ILT and the aneurysm wall. An isotropic constitutive model is a

Table 1. Mean and standard deviation (SD) of age, blood pressure, maximum diameter, Peak Wall Stress (PWS), Peak Wall Rupture Risk Index (PWRI), PWS-equivalent diameter (DPWS) and PWRI-equivalent diameter (DPWRI) of non-ruptured and ruptured cases. The number of cases in the different groups is denoted by *n*.

Non-ruptured				Ruptured											
<i>n</i>	Age (years)	Systolic/ diastolic pressure (mmHg)	Diam. (mm)	PWS (kPa)	PWRI	<i>D</i> _{PWS} (mm)	<i>D</i> _{PWRI} (mm)	<i>n</i> ^a	Age (y)	Systolic/ diastolic pressure (mmHg)	Diam. (mm)	PWS (kPa)	PWRI	<i>D</i> _{PWS} (mm)	<i>D</i> _{PWRI} (mm)
Female	44	72	144/81 (SD 9)	53	196 (SD 66)	0.59 (SD 0.29)	51 (SD 18)	63 (SD 23)	6	80 (SD 17)	71 (SD 12)	285 (SD 66)	1.07 (SD 0.30)	75 (SD 18)	100 (SD 21)
	159	72	142/80 (SD 8)	56	212 (SD 78)	0.46 (SD 0.23)	55 (SD 21)	52 (SD 18)	34	74 (SD 8)	82 (SD 18)	334 (SD 105)	0.99 (SD 0.46)	88 (SD 28)	92 (SD 29)
All	203	72	143/80 (SD 8)	55	208 (SD 76)	0.49 (SD 0.24)	55 (SD 20)	55 (SD 19)	40	74 (SD 10)	82 (SD 18)	336 (SD 107)	1.03 (SD 0.44)	89 (SD 29)	96 (SD 28)

^a The number of cases where blood pressure measurements could not be taken from the last admission before rupture is given in brackets.

common approximation for aneurysm tissue and assumes that the tissue’s mechanical properties do not depend on the orientation, i.e. the stress—strain responses of circumferential and longitudinal strips of tissue are identical. The strength of the aneurysm wall is inhomogeneous and the applied FE models consider a wall strength model that accounts for local wall weakening influenced by the ILT, gender, family history, and the ratio between the local diameter and the normal infrarenal aortic diameter.²⁷ Further details regarding the biomechanical AAA rupture risk assessment and specific modeling assumptions used by A4clinics are given elsewhere.^{25,28} A typical image showing the distribution of the rupture risk index (stress—strength ratio) in the aneurysm wall is illustrated in Fig. 1, and further details regarding the reproducibility of the analysis are reported elsewhere.^{29,30}

Data analysis

To quantify the change in PWS and PWRI between the different patient groups independently from the diameter, we introduced the mean population PWS and PWRI curve for non-ruptured AAAs thought to reflect the average (non-ruptured) patient. Here, “average” is understood in a purely mathematical sense. For this definition we considered a female percentage of 17, such that our average patient reflects the gender ratio of the UK small aneurysm trial.³ Specifically, the mean population PWS and PWRI curves as functions of the maximal diameter (i.e. which reflect the average patient) were generated by weighting female and male regression curves by 0.17 and 0.83, respectively, based on several clinical studies³ and served as reference for the average patient curve.

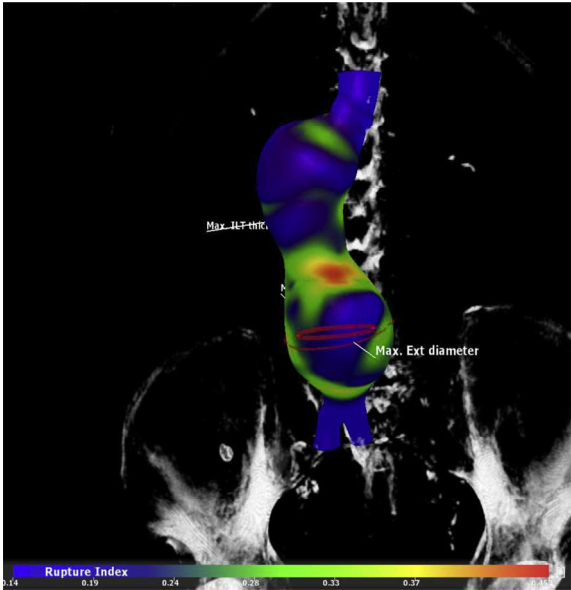


Figure 1. Color coded illustration of the rupture risk index distributed over the abdominal aortic aneurysm (AAA) wall. The peak wall rupture index (PWRI) represents the highest rupture index over the entire AAA wall between renal arteries and aortic bifurcation.

Table 2. Value for p from difference testing (Welch's t test) between non-ruptured and ruptured cases.

	Female	Male	All
Age	.282	.105	.078
Systolic/diastolic pressure	.474/.270	.313/.330	.309/.387
Diameter D	.115	<.001	<.001
Peak wall stress (PWS)	.009	<.001	<.001
Peak wall rupture index (PWRI)	.004	<.001	<.001
PWS-equivalent diameter D_{PWS}	.009	<.001	<.001
PWRI-equivalent diameter D_{PWRI}	.003	<.001	<.001

In order to compare with clinical studies, PWRI regression curves of ruptured and non-ruptured aneurysms were weighted according to the rupture prevalence² and plotted with respect to the diameter.

Statistical data analysis was performed with Mathematica (Wolfram Research Inc., Champaign, IL, USA). Normal distribution of the variables was tested using the Kolmogorov–Smirnov test. For hypothesis testing Welch's t test with the one-sided significance level of $p < .05$ was used.

RESULTS

General cohort characteristics

Maximum diameter (82 mm vs. 55 mm; $p < .001$), PWS (336 kPa vs. 208 kPa; $p < .001$), and PWRI (1.03 vs. 0.49; $p < .001$) were larger in the ruptured than in the non-ruptured cases. This was also seen in male and female subgroups, and further details are listed in Tables 1 and 2. The Kolmogorov–Smirnov test showed that the diameter was normally distributed in the ruptured groups (female, $p = .754$; male, $p = .749$; all, $p = .938$), whereas this was not the case for all non-ruptured groups ($p < .01$) (Table 3).

Relation between biomechanical indices and the maximum diameter

In all groups PWS and PWRI were scattered and increased with diameter, underlining the fact that the size is recognized by these biomechanical indices. A non-linear regression analysis demonstrated that PWS increases linearly and PWRI exponentially with diameter and had similar relative mean square errors in females and males (PWS regression, female/male = 0.046/0.045; PWRI regression, female/male = 0.091/0.067). Simplified theoretical considerations

that assume linearly increasing wall stress and linearly decreasing wall strength with relative expansion also point towards an exponential increase of PWRI with respect to the diameter.

For the non-ruptured aortas, male and female regression curves are shown in Fig. 2, indicating that PWS is similar, whereas PWRI differs between men and women. Indeed, PWRI increases faster in females than in males with respect to diameter; similar observations were made for the ruptured cases.

Relation between PWRI and the annual risk of rupture

The predicted progressive increase in the average patient's PWRI with diameter using our biomechanical model has the similar exponential appearance as the progressive increase in annual AAA rupture risk with diameter. Upper and lower estimates of the annual rupture risk were estimated by Brewster et al.² (based on several clinical studies), and are illustrated by the thin solid lines in Fig. 3, whereas the thick line represents the PWRI that were computed from the biomechanical analysis of our patient cohort. Note that the representation is also a translation from the PWRI to an estimated annual risk of rupture, for example a PWRI of 0.39, 0.53, 0.68, 0.95, and 1.23 corresponds to an annual rupture risk of 3.6%, 9.8%, 16.8%, 28.7%, and 41.4%, respectively.

Biomechanical estimates among patient groups

In order to compare biomechanical estimates among the different patient groups, the PWS- and PWRI-equivalent diameters, D_{PWS} and D_{PWRI} say, were introduced (Fig. 4). These diameters reflect the size of the average aneurysm that experiences the same estimates as the individual case. Subtracting the maximum diameter D from D_{PWS} or D_{PWRI} gives a risk measure $\Delta D_{PWS} = D_{PWS} - D$ or $\Delta D_{PWRI} = D_{PWRI} - D$ (Fig. 4) that can be used to compare among patient groups independently of the diameter (size) effect.

ΔD_{PWS} was similar in males and females (non-ruptured $p = .251$; ruptured $p = .358$) but was elevated by 7.5 mm ($p = .013$) in ruptured patients compared with the non-ruptured cases (Fig. 5A). This difference remained statistically significant in male ($\Delta D_{PWS} = 6.8$ mm; $p = .032$) but not in female ($\Delta D_{PWS} = 5.4$ mm; $p = .231$) subgroups.

The relation between PWRI and D_{PWRI} for the average patient is shown in Table 4, where a PWRI of 0.48 corresponds to a D_{PWRI} of 55 mm, the generally accepted indication for AAA repair in males. ΔD_{PWRI} was 13.2 mm

Table 3. Kolmogorov–Smirnov testing the normal distribution of parameters.

Significance level (p -value)	Non-ruptured			Ruptured		
	Female	Male	All	Female	Male	All
Diameter D	.004	<.001	<.001	.754	.749	.938
PWS-equivalent diameter D_{PWS}	.245	<.001	<.001	.639	.442	.245
PWRI-equivalent diameter D_{PWRI}	.077	<.001	<.001	.821	.174	.406
$\Delta D_{PWS} = D_{PWS} - D$.006	.084	.021	.220	.263	.097
$\Delta D_{PWRI} = D_{PWRI} - D$.732	.519	.008	.268	.773	.706

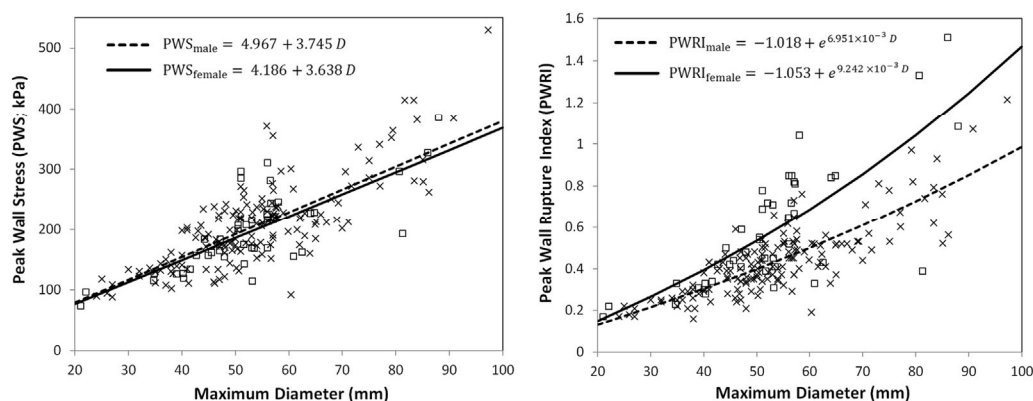


Figure 2. Development of peak wall stress (PWS) and peak wall rupture index (PWRI) with respect to the maximum diameter of non-ruptured abdominal aortic aneurysms (AAAs). Squares denote female and crosses male patients. Solid lines (female) and dashed lines (male) denote regression curves.

($p < .001$) and 17.9 mm ($p = 0.014$) higher in females than males for the non-ruptured and ruptured groups, respectively. Most important, ΔD_{PWRI} was elevated by 14.0 mm ($p < .001$) in ruptured patients when compared with the non-ruptured cases (Fig. 5B). This difference remained statistically significant in male ($\Delta D_{PWRI} = 14.1$ mm; $p < .001$) and female ($\Delta D_{PWRI} = 18.8$ mm; $p = .012$) subgroups.

Finally, in order to verify that these results are not biased by the difference in size of ruptured and non-ruptured groups more homogeneous (but still not diameter-matched) groups were tested. Specifically, non-ruptured cases that were smaller than 60 mm were excluded, which led to a subgroup analysis that contained 53 non-ruptured and 40 ruptured cases. Here, ΔD_{PWS} was elevated by 9.2 mm ($p = .003$) in the ruptured group (males 8.9 mm, $p = .011$; females 9.3, $p = .045$). Similarly, ΔD_{PWRI} was elevated by 20.0 mm ($p < .001$) in the ruptured group (males 17.3 mm, $p < .001$; females 21.2, $p = .118$).

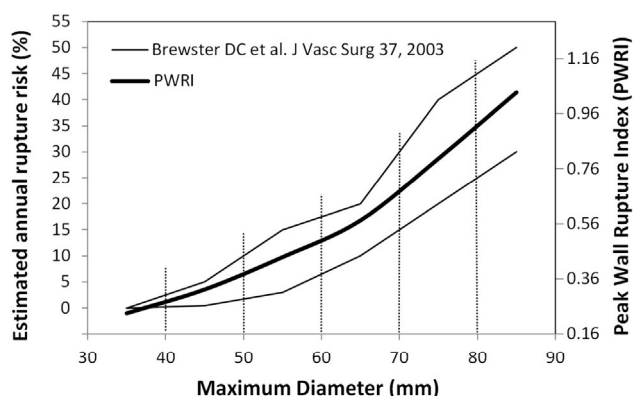


Figure 3. Progressive increase of annual rupture risk of abdominal aortic aneurysm (AAA) with respect to the maximum diameter. Thin solid lines represent upper and lower estimates² based on reported data. The thick solid line denotes peak wall rupture index (PWRI) based on a regression analysis of our patient cohort. PWRI has been adjusted for ruptured AAAs, i.e. regression curves for ruptured and non-ruptured cases were weighted according to reported rupture prevalence.²

DISCUSSION

Biomechanically analyzing a large patient cohort illustrated that PWS increases linearly whereas PWRI increases exponentially with the maximal diameter. These average trends were expected, since simpler biomechanical models like the inflated tube or sphere already predict a linear increase of PWS, whereas the wall weakening properties that are incorporated by PWRI explain the progressive increase of this index with diameter. The average trend curves were in turn used to introduce D_{PWS} and D_{PWRI} , that is equivalent maximum diameters of an average aneurysm that experiences the same PWS and PWRI, respectively.

A size-adjusted analysis showed that D_{PWS} and D_{PWRI} were increased by 7.5 mm and 14.0 mm respectively in ruptured cases when compared with non-ruptured controls. Although comparison was statistically significant, a large overlap between ruptured and non-ruptured cases was observed. Aneurysm rupture is to some extent a stochastic event, which, even in cases at relatively low risk of rupture, can be triggered by a high peak in blood pressure.

The present study agrees with previous ones showing that PWRI (or PWRI-based indices²⁷) discriminates better between ruptured and non-ruptured cases than PWS.^{25,26} Most important, however, D_{PWRI} links an individualized biomechanical rupture risk assessment with conclusions drawn from earlier clinical studies.

PWRI was higher in females than in males, which is a direct consequence of the lower strength of the female aneurysm wall, and a borderline increase of PWRI in females has been reported from a FE study in a small cohort.³¹ The present analysis used a larger number of patients and PWRI could significantly discriminate between males and females. In addition, the data predicted by our FE models suggested that a 50-mm AAA in females has the equivalent risk of rupture as a 63-mm aneurysm in males. This finding agrees with an earlier study suggesting that 50 mm in females compares with 60 mm in males.⁸

The present study has some limitations. FE models introduce numerous modeling assumptions and cannot completely reflect the biomechanics of the real aneurysm. In the present study, the constitution of aneurysm tissue

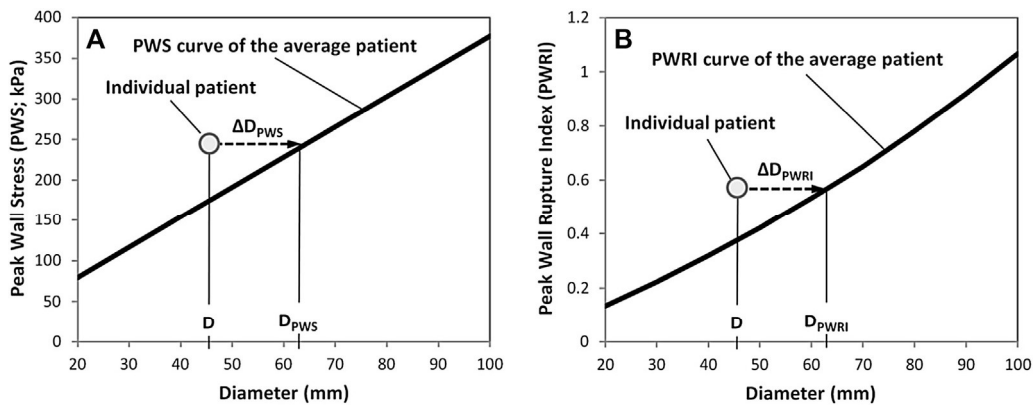


Figure 4. Definition of equivalent diameters for an individual abdominal aortic aneurysm (AAA) patient. (A) Peak wall stress (PWS) equivalent diameter D_{PWS} denotes the diameter of an average AAA that experiences the same PWS. (B) The peak wall rupture index (PWRI) equivalent diameter D_{PWRI} denotes the diameter of an average AAA that experiences the same PWRI.

including wall and ILT was captured by mean population data, but patient-specific elastic properties would have increased the accuracy of the stress prediction. Likewise, the present study considers an isotropic wall model, although it is known that the AAA wall exhibits mild anisotropy, which can influence PWS predictions.⁵ Constitutive data used by our, and by other, FE models of aneurysms is based on in vitro testing of the anterior wall, which may differ from the posterior wall, where aneurysm rupture is frequently observed.³² Finally, calcifications of the aneurysm wall were not specifically considered by our FE models. Although some attempts on integrating calcifications in FE models are reported in the literature, no consistent and reliable approach that accounts for the multiple influences of calcification on the aneurysm wall is known. With respect to the above-mentioned simplifications of our FE model, previous studies showed that stress predictions in aneurysms are relatively insensitive to changes in constitutive properties of the wall and the ILT,³³ and consequently the geometry seems to be the most critical property for wall stress estimates. Finally, it needs to be emphasized that potential modeling improvements do not necessarily improve the clinical benefit of the biomechanical AAA rupture risk assessment.

Wall strength and thickness are other major determinants in FE model-based risk assessment. Even though the present study could not consider a patient-specific wall thickness, at least the reported thinning behind a thicker ILT²¹ was implemented. It is also noted that failure tension (strength times wall thickness) remains almost constant in the AAA wall,³⁴ such that the computation of PWRI is much more insensitive to the local (and unknown) wall thickness than the PWS.

It should be emphasized that in contrast to diameter measurements that do not depend to a large extent on different methods, different model assumptions of the FE model can cause severely different predictions.³⁵ Consequently, the presented data in this study must always be seen in relation to the specific modeling assumptions.

Clinical studies have demonstrated that growth of the aneurysm³⁶ or the ILT²² might indicate an increased rupture risk, but the present study did not account for these types of risk. In addition, our FE models did not consider ILT fissures; although it is known that, if they involve a large volume or reach the aneurysm wall, wall stress is significantly elevated.³⁷

The applied retrospective grouping in ruptured and non-ruptured cases has drawbacks. For example AAA patients in

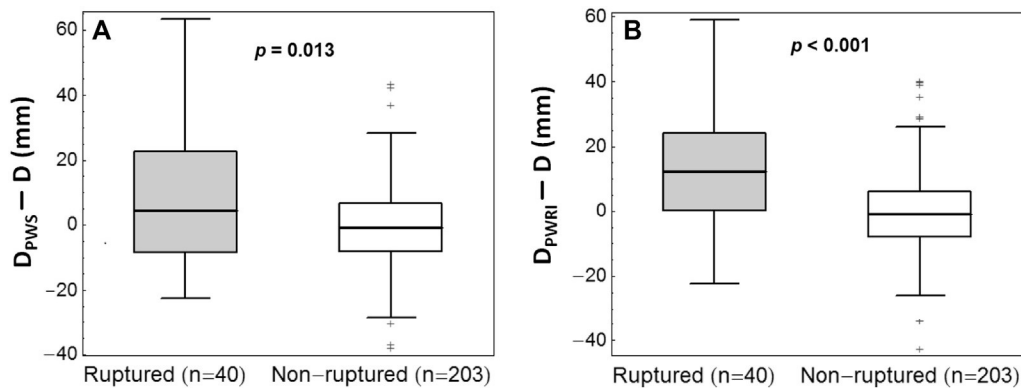


Figure 5. Difference between abdominal aortic aneurysm (AAA) maximum diameter D and their biomechanical equivalent diameters for ruptured (grey) and non-ruptured (white) cases. (A) Maximum diameter subtracted from the peak wall stress (PWS) equivalent diameter ($\Delta D_{PWS} = D_{PWS} - D$). (B) Maximum diameter subtracted from the peak wall rupture index (PWRI) equivalent diameter ($\Delta D_{PWRI} = D_{PWRI} - D$). The number of aneurysms for the different groups is given by n , and p denotes the one-sided p -value, respectively.

Table 4. Relation between peak wall rupture index (PWRI) and the PWRI-equivalent diameter D_{PWRI} . The D_{PWRI} reflects the maximum diameter of the average abdominal aortic aneurysm (AAA) patient experiencing the same PWRI, see also Fig. 4B for its definition.

PWRI	0.24	0.32	0.40	0.48	0.56	0.64	0.72	0.80	0.88	0.96
D_{PWRI} (mm)	32	40	48	55	62	69	75	81	87	93

the non-ruptured group could have ruptured after a short time if they would not have been repaired, while ruptured case would have ended up in the non-ruptured group if treated shortly before rupture.

CONCLUSIONS

The biomechanical rupture risk assessment quantitatively integrates many known risk factors, and hence supports a highly individualized risk assessment. The biomechanical risk for rupture is best expressed by the PWRI-equivalent diameter, which relates the individual case to the size of an average aneurysm at the same biomechanical risk for rupture. The PWRI-equivalent diameter allows for a size-independent discrimination between ruptured and non-ruptured aneurysms. Consequently, the PWRI-equivalent diameter should be included as an additional indication for elective AAA repair.

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CONFLICT OF INTEREST

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